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Original Research Article

Serum magnesium as a biochemical and pharmacological risk marker for arrhythmias in chronic cardiovascular disease

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Abstract

Purpose: *To estimate the point prevalence of hypomagnesemia among adults with chronic cardiovascular disease (CVD) and its association with arrhythmias, left ventricular ejection fraction (LVEF), and exposure to commonly prescribed cardiovascular medications.*
Methods: *This cross-sectional study was conducted at Al-Kindy Teaching Hospital, Baghdad, Iraq, from March 2023 to August 2024. The study included 200 adults with established CVD and 100 healthy controls. Serum magnesium was measured using a standardized colorimetric assay, with hypomagnesemia defined as < 1.8 mg/dL. Arrhythmias were assessed by 12-lead electrocardiography and LVEF by transthoracic echocardiography. Medication exposure was obtained from medical records and patient interviews.*
Results: *Hypomagnesemia was significantly more prevalent among patients with CVD compared with controls ($p < 0.001$) and independently associated with arrhythmias (odds ratio [OR] = 2.3; 95 % confidence interval [CI]: 1.4 – 3.8; $p = 0.001$). Each 0.1 mg/dL decrease in serum magnesium was associated with a 0.15 % reduction in LVEF ($\beta = -0.15$; 95 % CI: −0.25 to −0.05; $p = 0.002$). Furthermore, hypomagnesemia was more frequent among users of diuretics, proton pump inhibitors, angiotensin-converting enzyme inhibitors, and digoxin.*
Conclusion: *Hypomagnesemia was common among patients with CVD, and independently associated with arrhythmias.*

Keywords: *Arrhythmias, Biochemical risk marker, Cardiovascular disease, Hypomagnesemia, Magnesium, Medication safety*

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INTRODUCTION

Cardiovascular diseases (CVDs) are a leading cause of morbidity and mortality worldwide, accounting for approximately 17.9 million deaths annually. Despite advances in pharmacotherapy and interventional cardiology, arrhythmias, heart failure, and sudden cardiac death remain major clinical burdens. Established risk factors include hypertension, diabetes mellitus, dyslipidemia, and smoking, while disturbances in micronutrients, particularly magnesium

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deficiency, may also modify cardiovascular risk [1]. Magnesium is an essential intracellular cation and cofactor for more than 300 enzymatic reactions involved in cellular energy production, transmembrane ion transport, and protein biosynthesis. In the cardiovascular system, magnesium contributes to myocardial excitability, vascular smooth-muscle tone, endothelial function, calcium homeostasis, and myocardial repolarization. It also participates in adenosine triphosphate (ATP)-dependent reactions, actin–myosin cross-bridge cycling, and Na^+/K^+-ATPase activity. Furthermore, reduced serum magnesium may disturb transmembrane electrochemical gradients and contribute to ventricular ectopy, atrial fibrillation, QT prolongation, and impaired systolic function [2]. Epidemiological and clinical studies have reported an inverse relationship between circulating magnesium concentrations and adverse cardiovascular outcomes, including coronary heart disease, hypertension, heart failure, and cardiovascular mortality. These observations support interest in serum magnesium as a clinically accessible biochemical marker rather than merely an electrolyte measurement [3]. Magnesium status also has pharmacological implications. Several cardiovascular and related medicines influence magnesium homeostasis, while magnesium depletion may increase susceptibility to medication-related adverse effects, including arrhythmogenic effects. Loop and thiazide diuretics increase renal magnesium loss, proton pump inhibitors may reduce intestinal magnesium absorption, and hypomagnesemia may increase vulnerability to digoxin-related arrhythmogenic toxicity. These drug–electrolyte relationships suggest that magnesium status is valuable in medication-safety assessment during chronic cardiovascular pharmacotherapy [4]. Although magnesium has been studied in acute cardiovascular settings, less attention has been given to hypomagnesemia among stable adults with established CVD, particularly in Middle Eastern populations. Therefore, this study investigated the point prevalence of low serum magnesium among Iraqi adults with CVD and examined its independent association with electrocardiogram (ECG)-based arrhythmias, left ventricular ejection fraction (LVEF), and exposure to commonly prescribed cardiovascular medications.

METHODS

Study design and setting

This cross-sectional observational study was conducted at Al-Kindy Teaching Hospital, Baghdad, Iraq, from March 2023 to August 2024. Ethical approval was obtained from the Ethics Committee of Al-Kindy Teaching Hospital (approval no: AKTH-2023-112).

Written informed consent was obtained from all participants before enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki [5].

Study population

A total of 200 adults aged 18–75 years with established CVD, including coronary artery disease, heart failure, or chronic arrhythmias, were recruited from cardiology outpatient clinics.

A control group of 100 apparently healthy adults without a history of CVD was recruited from the local community during the same period.

Inclusion criteria

Participants were aged 18 – 75 years, had an established diagnosis of CVD confirmed by a cardiologist, and were clinically stable at the time of assessment.

Exclusion criteria

Participants with chronic kidney disease (CKD), with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m², significant hepatic impairment, pregnancy, current magnesium supplementation, acute infection, inflammatory state, or recent hospitalization within 4 weeks were excluded.

Sample size calculation

The sample size was estimated to detect a 15 % minimum difference in the prevalence of hypomagnesemia between CVD participants and controls with 80 % power at a two-sided α level of 0.05. A minimum of 180 participants with CVD was estimated.

As a result, 200 patients were included to account for possible missing data. The calculation was based on standard assumptions for comparing two independent proportions.

Data collection

Age, sex, body mass index (BMI), smoking history, and comorbidities were obtained through structured interviews and medical-record review. All participants underwent standardized clinical and laboratory assessment during the study visit.

Evaluation of biochemical parameters

Venous blood samples were collected in the morning after an overnight fast. Serum magnesium was measured using a standardized colorimetric assay on a Roche Cobas 6000 analyzer according to the manufacturer's instructions and hospital laboratory quality-control procedures. Hypomagnesemia was defined as serum magnesium concentration < 1.8 mg/dL (reference range was 1.8 – 2.3 mg/dL). Other laboratory measurements included serum potassium, serum calcium, serum creatinine, and fasting blood glucose. Estimated glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [6].

Cardiac assessment

Arrhythmia assessment

Arrhythmia was assessed using a resting 12-lead electrocardiogram (ECG). Rhythm abnormalities, including atrial fibrillation, premature ventricular contractions, and other major arrhythmias, were identified by a consultant cardiologist.

Cardiac function

LVEF was assessed by transthoracic echocardiography according to the American Society of Echocardiography guidelines [7]. An LVEF < 50 % indicated impaired systolic function. Echocardiographic measurements were performed by certified technicians who were blinded to laboratory findings.

Medication exposure assessment

Medication exposure was assessed by structured review of hospital records and confirmed during patient interviews. Recorded medication classes included loop and thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, digoxin, antiarrhythmic medications, proton pump inhibitors, and statins. Participants could be included in more than one medication category. Medication exposure was incorporated into subgroup and exploratory regression analyses to assess associations with magnesium status.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and compared using the independent-samples t-test. Categorical variables were expressed as frequencies and percentages, and compared using chi-square tests. Normality was assessed using the Shapiro–Wilk test. Non-parametric tests were considered when normality assumptions were not met. Multivariable logistic regression was used to assess the independent association between hypomagnesemia and arrhythmias, with adjustment for age, sex, BMI, smoking, serum potassium, serum calcium, and creatinine. Multivariable linear regression was used to assess the association between serum magnesium and LVEF. Analysis of medication exposure was exploratory and not interpreted as evidence of causality. Model assumptions, including linearity, residual independence, and absence of multicollinearity, were assessed; multicollinearity was evaluated using the variance inflation factor (VIF), with VIF < 5 considered acceptable. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

There was a significant difference in age, serum magnesium, hypomagnesemia, LVEF, and arrhythmias between the study and control groups (p < 0.001; Table 1).

Table 1: Baseline characteristics of study participants

Characteristic	Patients (n = 200)	Control (n = 100)	*P*-value
Age (years)	58.2±10.5	45.3±9.8	< 0.001
Male (%)	60	55	0.42
BMI (kg/m²)	28.1±4.7	27.8±4.5	0.65
Smokers (%)	25	10	0.002
Magnesium (mg/dL)	1.7±0.4	2.0±0.3	< 0.001
Hypomagnesemia (< 1.8 mg/dL; %)	42	15	< 0.001
LVEF (%)	45.6±8.9	62.3±5.2	< 0.001
Arrhythmias (%)	30	5	< 0.001

Body mass index (BMI), left ventricular ejection fraction (LVEF)

Independent association between hypomagnesemia and arrhythmias

In multivariable logistic regression adjusted for age, sex, BMI, smoking status, serum potassium, serum calcium, and creatinine, hypomagnesemia was significantly associated with increased odds of arrhythmias (odds ratio [OR] = 2.3; 95 % confidence interval [CI]: 1.4–3.8; p = 0.001; Table 2).

Association between serum magnesium and cardiac function

Serum magnesium was significantly associated with LVEF ($p < 0.05$). Each 0.1 mg/dL decrease in serum magnesium corresponded to a 0.15 % reduction in LVEF (β = −0.15; 95 % CI: −0.25 to −0.05; p = 0.002).

Medication exposure and hypomagnesemia

Among patients with CVD, hypomagnesemia was significantly more frequent in diuretic, proton pump inhibitor, ACE inhibitor, and digoxin users ($p < 0.05$; Table 3).

DISCUSSION

The study demonstrated that hypomagnesemia is common among adults with chronic CVD and is associated with arrhythmogenic risk and impaired systolic function. More than 40 % of patients with CVD had serum magnesium below the defined clinical threshold, compared with 15 % of controls. The association with arrhythmias remained significant after adjustment for major demographic and biochemical confounders, supporting the potential value of serum magnesium as a clinically relevant risk marker [8]. The findings are biologically plausible because magnesium contributes to transmembrane ionic stability, ATP-dependent reactions, calcium handling, and myocardial repolarization. Reduced magnesium availability may therefore increase electrophysiological instability and contribute to atrial or ventricular rhythm disturbances [9].

The observed relationship between lower serum magnesium and reduced LVEF is also consistent with the role of magnesium in myocardial energy metabolism and actin–myosin cross-bridge cycling [10]. Findings from medication exposure further supported the pharmacological relevance of magnesium status. Hypomagnesemia was more frequent among users of diuretics, proton pump inhibitors, ACE inhibitors, and digoxin. These observations are compatible with the broader cardiovascular and pharmacological relevance of magnesium described in a previous study [11], but the exploratory and cross-sectional design prevents causal interpretation. In particular, disease severity, polypharmacy, treatment duration, and confounding by indication may influence the observed associations. From a clinical perspective, serum magnesium is a relatively accessible laboratory parameter that may complement cardiovascular risk assessment, particularly in patients receiving long-term medications capable of disturbing electrolyte balance. However, serum magnesium reflects extracellular magnesium and may not fully represent intracellular stores. Resting 12-lead ECG may also miss intermittent arrhythmias, and the substantial age difference between patients and controls may have introduced residual confounding. The present findings also have implications for clinical pharmacy practice.

Table 2: Independent association between hypomagnesemia and arrhythmias

Outcome	Association	Estimate (95 % CI)	*P*-value
Arrhythmias	Low compared to normal magnesium	OR = 2.3 (1.4–3.8)	0.001
LVEF	Per 0.1 mg/dL magnesium decrease	β = −0.15 (−0.25 to −0.05)	0.002

Left ventricular ejection fraction (LVEF), odds ratio (OR), confidence interval (CI), regression coefficient (β)

Table 3: Association between medication exposure and hypomagnesemia among patients with CVD

Drug class	Patients using drug (n)	Hypomagnesemia among users (%)	*P*-value
Diuretics (loop/thiazide)	85	72	0.001
Proton pump inhibitors	68	63	0.004
ACE inhibitors	52	44	0.031
Beta-blockers	49	29	0.098
Digoxin	16	81	0.007
Statins	77	21	0.220

Angiotensin-converting enzyme (ACE). Participants could be included in more than one medication category. Medication-exposure analyses were exploratory and should not be interpreted as evidence of causal drug effects

Patients receiving loop or thiazide diuretics may experience increased renal magnesium losses, while prolonged proton pump inhibitor therapy has been associated with reduced intestinal magnesium absorption. In patients receiving digoxin, electrolyte disturbances may increase vulnerability to adverse cardiac effects. These relationships do not establish that the medications caused the low magnesium concentrations, because underlying cardiovascular conditions and differences in treatment intensity may themselves influence electrolyte status. Nevertheless, identifying patients with low magnesium may help clinicians recognize a potentially modifiable biochemical abnormality when evaluating arrhythmias or changes in cardiac function.

From a pharmacotherapeutic perspective, magnesium assessment may therefore be particularly relevant when unexplained rhythm disturbances occur in patients receiving medications that affect electrolyte balance. Interpretation should remain individualized and should consider renal function, concomitant electrolyte abnormalities, treatment duration, and overall clinical context. The findings supported magnesium measurement as an adjunct, rather than a replacement, for established cardiovascular assessment and medication review [12]. Other limitations include the absence of dietary magnesium intake, urinary magnesium excretion, intracellular magnesium measurements, and inflammatory markers. The control group was also younger than the study group, although age and other clinically relevant variables were included in multivariable models. In addition, medication-exposure analyses were exploratory and were not fully adjusted for disease severity, polypharmacy, or duration of therapy [13]. These factors may have contributed to observed medication associations. Longitudinal and interventional studies are needed to determine whether correction of hypomagnesemia improves electrophysiological stability, myocardial function, and long-term cardiovascular outcomes. The regional context is also relevant.

Evidence from Middle Eastern populations remains comparatively limited, and differences in dietary patterns, medication use, and healthcare delivery may influence magnesium status. The present study used data from an Iraqi clinical population and integrated laboratory findings with electrocardiographic, echocardiographic, and medication-exposure information. This combined approach may help place serum magnesium within a broader framework of biochemical monitoring and pharmacological risk assessment [14,15].

The association between hypomagnesemia and arrhythmias should nevertheless be interpreted cautiously. Magnesium participates in cardiac ion-channel regulation and intracellular calcium handling, but the cross-sectional design cannot establish whether low magnesium preceded the arrhythmia, resulted from the disease state, or reflected another unmeasured factor. Similarly, the association with LVEF does not demonstrate that magnesium deficiency directly caused impaired systolic function. These distinctions are important when translating observational findings into clinical recommendations. The findings therefore supported further investigation rather than a claim that serum magnesium alone predicts cardiovascular outcomes [16]. Future studies, including interventional trials, are needed to determine the correlation between documented hypomagnesemia and cardiac outcomes [17].

Routine serum magnesium monitoring may be considered in patients with chronic CVD, particularly those receiving medications that alter magnesium homeostasis, such as diuretics, proton pump inhibitors, or digoxin. Magnesium measurement may complement cardiovascular risk stratification by identifying patients with a greater likelihood of arrhythmias or impaired systolic function. Clinical pharmacists and other healthcare professionals should consider potential drug–electrolyte relationships when evaluating unexplained arrhythmias, reduced therapeutic safety, or suspected medication-related adverse effects. Magnesium status may be incorporated into individualized pharmacotherapy decisions alongside renal function and other electrolyte measurements. Prospective longitudinal and interventional studies are recommended to determine whether correcting hypomagnesemia improves electrophysiological stability, myocardial performance, and long-term cardiovascular outcomes.

Limitations of the study

The study only supported further investigation and did not conclude that serum magnesium measurements alone predict cardiovascular outcomes. Future studies should include repeated magnesium measurements, longer electrocardiographic monitoring, more detailed assessment of medication duration and dose, dietary intake, urinary magnesium excretion, and, where feasible, measures that better reflect intracellular magnesium status. Interventional

trials would be particularly valuable for determining whether correction of documented hypomagnesemia produces measurable improvements in cardiac rhythm or ventricular function.

CONCLUSION

Hypomagnesemia is common in chronic CVD and is associated with increased arrhythmogenic risk and impaired systolic function. The findings support the potential value of routine magnesium assessment as part of comprehensive chronic cardiovascular disease management.

DECLARATIONS

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Ethical approval

Approval was obtained from the Ethics Committee of Al-Kindy Teaching Hospital, Iraq (approval no: AKTH-2023-112).

Use of artificial intelligence/large language models

The authors confirm that AI-based tools were used solely for language editing and manuscript polishing purposes (e.g., grammar, phrasing, and clarity). No AI tools were used to generate content, interpret data, or influence study design, results, or conclusions. All intellectual contributions, study analyses, and interpretations reported in the manuscript are the original work of the authors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare no conflict of interest.

Contribution of authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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